UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,583	02/05/2001	Karl-Hermann Schlingensiepen	P66141US0	7033

136 7590 07/14/2004

JACOBSON HOLMAN PLLC
400 SEVENTH STREET N.W.
SUITE 600
WASHINGTON, DC 20004

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,583	SCHLINGENSIEPEN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-25-01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 5-5-04.

Claims 1-13 are pending in the instant application.

Election/Restrictions

Claim 6 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5-5-04.

Applicant's election with traverse of Group I in the reply filed on 5-5-04 is acknowledged. The traversal is on the ground(s) that the different Groups have the common effect of blocking signal pathways of substances negatively affecting the immune response, and because the immuno-suppressors claimed are very specific linking elements for the treatment of infectious diseases. This is not found persuasive because the compositions and methods of Group II, drawn to methods of treating neoplasms comprising the administration of an antibody inhibitor of a substance negatively affecting an immune response, require materially different and distinct methods steps from the elected Group I: administration of antibodies (Group II); and administration of an oligonucleotide inhibitor (Groups I and III). The antibodies and oligonucleotides provide inhibition in different and distinct ways (e.g. antibodies sterically inhibit receptor binding or post translational modifications required for target molecule activation; antisense target a gene and inhibit its expression). Likewise the restriction requirement of electing a single antisense oligonucleotide, as well as a single immuno-stimulator

is proper because the array of compositions claimed are each chemically and functionally distinct: each antisense oligonucleotide targets a different target molecule or target region; and each stimulator is chemically, biologically and functionally different and distinct: GM-CSF, SCF, CSF, IFN, FLT-3 ligand, MCP-1, and the various interleukins claimed all impart and/or elicit different biological effects (e.g. IL-2 leads to B cell differentiation and myeloid cell development; IL-4 leads to B cell activation, IgE production and antibody class switching; GM-CSF induces eosinphil, basophil, monocyte and macrophage production).

Groups I and II, drawn to compositions and methods for treating neoplasms, are distinct from Groups III and IV, drawn to compositions and methods for treating infectious diseases, because the biological outcome of treating neoplasms is different from the biological outcome of treating infectious diseases, and each outcome requires materially different and distinct mechanisms: treating neoplasms requires a recognition and immune defense by the body against its own neoplastic cells (Groups I, II); treating infectious diseases requires a recognition and immune defense by the body against a foreign infectious agent (e.g. virus, bacteria).

The requirement of restricting between Groups I, II, III and IV is still deemed proper and is therefore made FINAL.

Claims 9 and 10, however, have been rejoined in examining Group I, and claims 1-5, 7-13, drawn to compositions and methods for treating neoplasms in an organism comprising the administration of antisense of SEQ ID NO: 7 and a tumor cell extract have been examined as set forth in the Office action below.

Claims 1-5, 7-13 have been examined within the limitations of the elected Group as indicated below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 8, 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5 and 10, line 1, refer to figures. Applicant is required to describe the claimed invention without referring to figures, if possible. See MPEP § 608.01(m).

Regarding claim 8, line 2, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

In claim 11, line 3, it is unclear what "having the sequence" is referring to (e.g. does this refer to target sequences shared by all the TGF family members claimed?).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of TGF-beta expression comprising the administration of antisense oligonucleotides, and for treating a brain neoplasia comprising the administration of an antisense and IL-2, which antisense targets and inhibits the expression of TGF-beta 2 as taught previously by Fakhrai et al (see the 102 rejection below), does not reasonably provide enablement for the targeting and inhibition of the TGF-beta family in vivo using antisense of SEQ ID NO: 7 or optionally in combination with a tumor cell extract, and which provides for treatment effects for neoplasia in an organism The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods treating neoplasia or hyperproliferative diseases in a subject comprising the administration of antisense of SEQ ID NO: 7 and optionally further comprising the administration of a tumor cell extract. The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke

also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Likewise, Peracchi cautions investigators about the problems of achieving in vivo efficacy using oligonucleotide based approaches: "Much progress has been made towards understanding the structure and mechanism of these catalysts [ribozymes]...Despite this, it is not yet clear whether these molecules can be developed into clinically useful pharmaceutical preparations." (See the abstract on page 47). Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of

the ribozyme remains one of the major hurdles in the field." (See text on page 51).

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting TGF-beta family of genes in an organism comprising the administration of SEQ ID NO: 7, nor for treating neoplasia in a subject comprising the administration of this antisense and a tumor cell extract. The specification teaches the in vitro inhibition of TGF-beta expression using antisense. The specification also teaches the in vitro lysis of tumor cells following administration of antisense, GM-CSF and IL-4. One skilled in the art would not accept on its face the examples given in the specification of the in vitro inhibition of TGF-beta expression using antisense, or the in vitro lysis of tumor cells following administration of GM-CSF and IL-4 as being correlative or representative of the successful treatment of neoplasia in an organism in view of the lack of guidance in the specification and known unpredictability associated with inhibition of a target gene in an organism using antisense and optionally additionally using tumor cell extract and further whereby treatment effects are provided for any neoplasia in that organism.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods treating neoplasia or hyperproliferative diseases in a subject comprising the administration of SEQ ID NO: 7 and a tumor cell extract. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target TGF-

beta sequence for antisense of SEQ ID NO: 7 in combination with administration of a tumor cell extract) whereby TGF-beta family gene expression is inhibited in cells in vivo and treatment effects are provided for any neoplasia. Since the specification fails to provide any particular guidance for targeting appropriate cells harboring the target TGF-beta genes using antisense of SEQ ID NO: 7 in an organism, and additionally comprising the administration of a tumor cell extract, whereby treatment effects for any neoplasia are provided, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 7, 8, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Fakhrai et al.

Fakhrai et al (PNAS 93: 2909-2914, 1996) teach compositions and methods to treat a brain neoplasia comprising the administration of an antisense

that targets and inhibits the expression of TGF-beta 2, which is a substance that negatively affects an immune response, and further comprising the administration of IL-2, which is an immuno-stimulator (see text on p. 2909, text and table 1 on p. 2910; and discussion on p. 2912-2913)..

Claims 1-4, 7, 8 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Caniggia et al.

Caniggia et al (USPN 6,376,199) teach compositions comprising at least one antisense that targets and inhibits the expression of TGF-beta, which is a substance that negatively affects an immune response, and further comprising at least one immuno-stimulator, including GM-CSF (see col. 12, line 42-col.13, line 45).

Allowable Subject Matter

SEQ ID NO: 7 is free of the prior art searched.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

7-7-04

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600